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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/696,676	10/29/2003	Keith L. Black	67789-503	8501

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	**PAPER NUMBER**
1635	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/04/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/696,676	BLACK ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,110-118,121-173,176-200 and 204-221* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *184,185,187,191,199,200 and 204-219* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/27/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 1,110-118,121-173,176-183,186,188-190,192-198,220 and 221.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/27/07 has been entered.

Claims 119, 120, 174, and 175 were canceled, and claims 206-221 were added as requested.

Newly submitted claims 220 and 221 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims 220 and 221 are related to the elected products as methods of using the products inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). Although the elected composition can be used in the methods of claims 220 and 221, its use is not limited to administration to a mammal for delivering a medicant to an abnormal brain region. In the instant case the claimed compositions can be used to carry out *in vitro* assays to examine the biological effect of the drug on cells in culture. Thus, the methods of the invention of claims 220 and 221 are patentably distinct from the elected composition..

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 220 and 221 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 1, 110-118, 121-173, 176-200, and 204-221 are pending.

Claims 1, 110-118, 121-173, 176-183, 186, 188-190, 192-198, 220 and 221 are withdrawn from consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention or species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 5/2/06.

Claims 206, 207, 209-211, 213, 215, 216, and 218, when examined to the extent that they read on the elected species of cytokines, are free of the art and off all rejections under 35 USC 101 and 112. Accordingly, the office has chosen a second species for examination in these claims, i.e. diagnostic agents. Claim 119 is rejoined.

Claims 184, 185, 187, 191, 199, 200, and 204-219 are under consideration in this Office Action.

Rejections not reiterated from the previous Action are withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 184, 185, 187, 191, 200, 208, 212, 214, and 217 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for calcium-activated potassium channel agonists such as NS-1619 and 1-EBIO, does not reasonably provide enablement for the use of a guanylyl cyclase activating protein as a calcium-activated potassium channel agonist. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims have been amended to recite that "guanylyl cyclase activating protein" is a calcium-activated potassium channel agonist. The specification as filed also implies that this is the case at page 10, lines 14-21. The claims as amended are not adequately enabled because the specification fails to teach how to use a guanylyl cyclase activating protein as a calcium-activated potassium channel agonist.

Robertson et al (Am. J. Physiol. 265 (1 pt 1): C299-303, 1993, of record) taught that cyclic GMP protein kinase (cGMP-PK) activates Ca-activated potassium channels (K_{Ca} channels) in cerebral artery smooth muscle cells. Therefore it is conceivable that activators of guanylate cyclase could indirectly act as K_{Ca} channel agonists by increasing intracellular cGMP and subsequently activating cGMP-PK. However, the prior art also taught that guanylyl cyclase activating proteins (GCAPs) interact with the intracellular domain of guanylyl cyclase, and not the extracellular domain. See e.g. Ermilov JBC 276(51): 48143-8 2001, abstract). Thus one of skill in the art would not expect that extracellular application of a GCAP, as envisioned in the specification, would result in activation of guanylyl cyclase. While the prior art taught K_{Ca} channel

agonists that act extracellularly, such as bradykinin, NS-1619, and 1-EBIO, the prior art of record does not disclose the use of a GCAP to activate K_{Ca} channels by either an intracellular or extracellular mechanism. In the study of GCAP function, the prior art generally taught the application of GCAPs to isolated membrane fractions that allow molecular access to either side of the membrane without need to enter a cell by traversing the membrane. See e.g. Ermilov (2001) paragraph bridging columns 1 and 2 on page 48144, Hwang et al (Biochem. 41:13021-13028, 2002) see paragraph bridging columns 1 and 2 on page 13022, or Frins et al (J, Biol. Chem. 271(14): 8022-8027, 1996) at page 8023, column 2, fifth full paragraph. There is no evidence of record that suggests, nor any reason to believe, that extracellularly administered GCAPS would activate a cellular guanylate cyclase because the intracellular guanylate cyclase domains with which GCAPS naturally interact would not be accessible to extracellularly administered GCAPs. Neither the specification nor the prior art of record provides any guidance or examples as to how one could induce cellular uptake of a GCAP to allow an extracellularly administered GCAP to interact with the appropriate intracellular guanylate cyclase domain such that guanylate cyclase is activated. Because GCAPS act intracellularly to activate guanylyl cyclases, one of skill in the art could not use them for their intended purpose of activating K_{Ca} channels absent some guidance as to how to cause them to be internalized into a cell. Absent such guidance, and in view of the state of the art, the level of unpredictability in the art, and the lack of working examples in the specification, the skilled artisan would have to perform undue experimentation in order to use a GCAP as a K_{Ca} channel agonist.

Response to Arguments

Applicant's arguments filed 2/27/07 have been fully considered but they are not persuasive.

Applicant addresses the rejection at pages 18 and 19 of the response. Applicant asserts that extracellularly administered GCAPs can activate cellular guanylate cyclase, relying for support on Currie (1984) and the Sigma-Aldrich product description for Atriopeptin II. This is unpersuasive. The Currie reference does not mention any effect of Atriopeptins on guanylyl cyclase, and Applicant has not pointed to any specific passage as doing so. Furthermore, atriopeptins and other natriuretic peptides are not GCAPs. "Guanylyl cyclase activating protein" (GCAP) is a term of art that refers to an intracellular, calcium binding, EF-hand domain-containing class of proteins that stimulate guanylyl cyclase. See first sentence of Ermilov (2001) abstract (of record). There is no evidence of record that the term "GCAP" refers to any extracellular peptide.

Applicant also asserts that GCAPs may cross the plasma membrane, relying for support on Sokal (2002). Sokal presents no evidence of this, and in fact supports the position of the Office. Sokal taught fusion proteins between intracellular guanylyl cyclase domains and GCAPs. The activity of these proteins on guanylyl cyclases was assayed, not in whole cells, but in membrane preparations that allow access to either side of the membrane. See abstract and page 4, third paragraph. Why would Sokal bother to use membrane preparations if the fusion proteins were capable of crossing the

cell membrane? There is nothing in Sokal to support Applicant's allegation that any GCAP traversed a membrane.

Applicant's assertion at page 19 that "cells frequently possess mechanisms for the uptake of proteins and one of skill in the art would appreciate that extracellularly administered guanylyl cyclase activating protein may cross the plasma membrane to activate guanylyl cyclase" is unsupported and squarely at odds with the evidence of record.

Applicant asserts at page 19 that a GCAP may interact with the extracellular domain of guanylyl cyclase, relying for support on Rambotti (2002). This is unpersuasive because Rambotti does not address GCAPs in any way. Instead, Rambotti is concerned with natriuretic peptides and calcium sensor peptides. As discussed above, "guanylyl cyclase activating protein" (GCAP) is a term of art that denotes intracellular proteins (see abstract of Ermilov, see Hwang (2002) at page 13021, column 1, lines 1-12, and see abstract of Frins (1996). See also paragraph bridging pages 85 and 86, and page 86, first full paragraph of Rambotti (Mol. Cell. Biochem 230: 85-96, 2002). Fro these reasons the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 200, 205, and 210 are rejected under 35 U.S.C. 103(a) as being unpatentable over Veltkamp et al (Stroke 29: 837-843, 1998).

Veltkamp taught methods of assaying the effects of NS-1619 on the vascular response to NMDA after hypoxia and ischemia. See abstract.

Veltkamp did not teach the organization of NS-1619 and NMDA into a kit. However, it would have been obvious to one of ordinary skill in the art at the time of the invention to organize these agents into a kit because one of skill in the art appreciates that organizing experimental reagents prior to use is standard laboratory practice which reduces the frequency of errors.

The text of Veltkamp, could be considered to be instructions for how to use the kit. However, it is noted that the "instructions for use" limitation does not receive patentable weight because the courts have repeatedly found that the application of particular printed matter to an old article cannot render the article patentable. For example, in the Opinion Text of *In re Haller*, 73 USPQ 403 (CCPA 1947), the court stated "[w]hether the statement of intended use appears merely in the claim or in a label on the product is immaterial so far as the question of patentability is concerned." The court in *In re Gulack* (217 USPQ 401 (1983)) found that printed matter has no patentable weight unless the printed matter affects the function of the product claimed. Also, see in *In re Ngai* (70 USPQ2D 1862 (2004)).

Claims 200, 205, and 211 are rejected under 35 U.S.C. 103(a) as being unpatentable over Devor et al (Am. J. Physiol. 271(5): L775-84, 1996).

Devor evaluated the effects of 1-EBIO and charybdotoxin on chloride ion secretion in T84 monolayers. See abstract.

Devor did not teach the organization of 1-EBIO into a kit. However, it would have been obvious to one of ordinary skill in the art at the time of the invention to organize these agents into a kit because one of skill in the art appreciates that organizing experimental reagents prior to use is standard laboratory practice which reduces the frequency of errors.

The text of Devor could be considered to be instructions for how to use the kit. However, it is noted that the "instructions for use" limitation does not receive patentable weight because the courts have repeatedly found that the application of particular printed matter to an old article cannot render the article patentable. For example, in the Opinion Text of *In re Haller*, 73 USPQ 403 (CCPA 1947), the court stated "[w]hether the statement of intended use appears merely in the claim or in a label on the product is immaterial so far as the question of patentability is concerned." The court in *In re Gulack* (217 USPQ 401 (1983)) found that printed matter has no patentable weight unless the printed matter affects the function of the product claimed. Also, see in *In re Ngai* (70 USPQ2D 1862 (2004)).

Claims 184, 199, 200, 204-206, 210, 214, 215, and 219 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gribkoff et al (Molecular Pharmacology, (1996 Jul) Vol. 50, No. 1, pp. 206-17).

Gribkoff taught the simultaneous use of NS-1649 with iberiotoxin, phloretin, or paxilline. See abstract, paragraph bridging pages 212 and 213, and first full paragrpah on page 213.

It would have been obvious to one of ordinary skill in the art at the time of the invention to make a pharmaceutical composition comprising NS-1649 and any of iberiotoxin, phloretin, or paxilline for simultaneous use in the method of Gribkoff. One would have been motivated to do so as a matter of convenience to allow simultaneous administration of these agents. Iberiotoxin, phloretin, and paxilline are considered to be diagnostic agents because their use allows the detection of large-conductance calcium-activated potassium channels.

Gribkoff did not teach the organization of NS-1619, and iberiotoxin, phloretin, and paxilline into a kit. However, it would have been obvious to one of ordinary skill in the art at the time of the invention to organize these agents into a kit because one of skill in the art appreciates that organizing experimental reagents prior to use is standard laboratory practice which reduces the frequency of errors.

The text of Gribkoff, could be considered to be instructions for how to use the kit. However, it is noted that the "instructions for use" limitation does not receive patentable weight because the courts have repeatedly found that the application of particular printed matter to an old article cannot render the article patentable. For example, in the Opinion Text of *In re Haller*, 73 USPQ 403 (CCPA 1947), the court stated "[w]hether the statement of intended use appears merely in the claim or in a label on the product is immaterial so far as the question of patentability is concerned." The court in *In re*

Gulack (217 USPQ 401 (1983)) found that printed matter has no patentable weight unless the printed matter affects the function of the product claimed. Also, see in *In re Ngai* (70 USPQ2D 1862 (2004)).

Claims 184, 199, 200, 204, 205, 207, 211, 214, 216, and 219 are rejected under 35 U.S.C. 103(a) as being unpatentable Ayotunde et al (Eur. J. Pharm. 379: 151-159, 1999).

Ayotunde taught the simultaneous use of 1-EBIO and NG-nitro-L-arginine methyl ester (L-NAME). See abstract.

It would have been obvious to one of ordinary skill in the art at the time of the invention to make a pharmaceutical composition comprising both L-NAME and 1-EBIO for simultaneous use in the method of Ayotunde. One would have been motivated to do so as a matter of convenience to allow simultaneous administration of these agents. L-NAME is considered to be a diagnostic agent because its use allows the detection of nitric oxide synthase, as L-NAME is an inhibitor of that enzyme.

Ayotunde did not teach the organization of 1-EBIO and L-NAME into a kit. However, it would have been obvious to one of ordinary skill in the art at the time of the invention to organize these agents into a kit because one of skill in the art appreciates that organizing experimental reagents prior to use is standard laboratory practice which reduces the frequency of errors.

The text of Ayotunde, could be considered to be instructions for how to use the kit. However, it is noted that the "instructions for use" limitation does not receive

patentable weight because the courts have repeatedly found that the application of particular printed matter to an old article cannot render the article patentable. For example, in the Opinion Text of *In re Haller*, 73 USPQ 403 (CCPA 1947), the court stated "[w]hether the statement of intended use appears merely in the claim or in a label on the product is immaterial so far as the question of patentability is concerned." The court in *In re Gulack* (217 USPQ 401 (1983)) found that printed matter has no patentable weight unless the printed matter affects the function of the product claimed. Also, see in *In re Ngai* (70 USPQ2D 1862 (2004)).

Claims 184, 199, 200, 204, 205, 209, 213, 214, 218, and 219 are rejected under 35 U.S.C. 103(a) as being unpatentable over Becker et al (Nitric Oxide: Biology and Chemistry, 3(1): 55-66, 1999).

Becker taught the simultaneous use of YC-1 and 2-(N,N-diethylamino)-diazenolate-2-oxide (DEA) and the simultaneous use of YC-1 and sodium nitroprusside (SNP). See abstract and e.g. Fig. 4.

It would have been obvious to one of ordinary skill in the art at the time of the invention to make a pharmaceutical composition comprising both YC-1 and either DEA or SNP for simultaneous use in the method of Becker. One would have been motivated to do so as a matter of convenience to allow simultaneous administration of these agents. DEA and SNP are considered to be diagnostic agents because their use allows the detection of guanylyl cyclase because they stimulate activity of that enzyme (see abstract).

Becker did not teach the organization of YC-1, DEA, and SNP into a kit. However, it would have been obvious to one of ordinary skill in the art at the time of the invention to organize these agents into a kit because one of skill in the art appreciates that organizing experimental reagents prior to use is standard laboratory practice which reduces the frequency of errors.

The text of Becker, could be considered to be instructions for how to use the kit. However, it is noted that the "instructions for use" limitation does not receive patentable weight because the courts have repeatedly found that the application of particular printed matter to an old article cannot render the article patentable. For example, in the Opinion Text of *In re Haller*, 73 USPQ 403 (CCPA 1947), the court stated "[w]hether the statement of intended use appears merely in the claim or in a label on the product is immaterial so far as the question of patentability is concerned." The court in *In re Gulack* (217 USPQ 401 (1983)) found that printed matter has no patentable weight unless the printed matter affects the function of the product claimed. Also, see in *In re Ngai* (70 USPQ2D 1862 (2004)).

Response to Arguments

Applicant's arguments filed 8/27/07 have been fully considered but they are not persuasive.

Applicant addresses the obviousness rejections over Veltkamp and Devor at pages 19-22 of the response. Applicant argues that these references do not teach that administration of the agonist and the medicant increases permeability of a capillary or

arteriole". This is unpersuasive because the effects of the compositions are inherent in their structures. NS-1619 and E1BIO inherently have the property of increasing permeability of capillaries and arterioles.

Applicant argues that Veltkamp does not provide any motivation to organize NS-1619 into a kit. However, it would have been obvious to one of ordinary skill in the art at the time of the invention to organize these agents into a kit because one of skill in the art appreciates that organizing experimental reagents prior to use is standard laboratory practice which reduces the frequency of errors. Applicant also argues that NMDA is not a medicant. This is unpersuasive because NMDA has well recognized pharmacological effects as a neurotransmitter, as admitted in Applicants response at the bottom of page 20. The term "medicant" has been given its broadest reasonable interpretation, in the absence of a limiting definition in the specification, and is considered to embrace any pharmacologically active substance. Applicant raises similar arguments, regarding the Devor reference. These arguments are unpersuasive for similar reasons, i.e. it is obvious to organize reagents in order to reduce errors, and charybdotoxin is a medicant because it has a well recognized pharmacological effect.

Regarding Applicant's request for rejoinder, because claims 204 and 205 are not allowable, method claims corresponding to these claims will not be rejoined at this time.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, J. Douglas Schultz, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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